Electrophilic Fluorination of Some Steroidal α,β-Unsaturated Ketones

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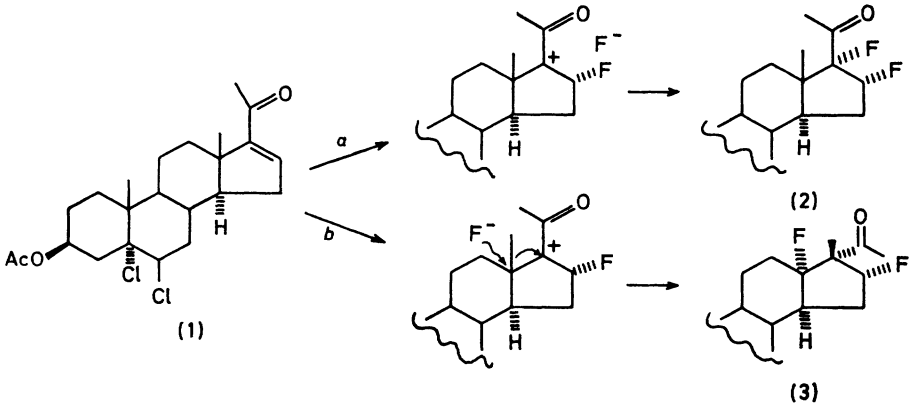
3β-Acetoxy-5α,6β-dichloropregn-16-en-20-one (1), on treatment with elemental fluorine at low temperature, gave the 16α,17α-difluoro-adduct (2) and, by rearrangement, the 13α,16α-difluoro-17β-methyl derivative (3). The adduct (2) was subsequently converted *via* a short, efficient synthetic sequence into 16α,17α-difluoroprogesterone (5). In contrast, fluorination of 21-acetoxypregna-1,4,16-triene-3,11,20-trione (6) afforded the corresponding 16α,17α-difluoro-adduct (8) in low yield. Similarly, androsta-1,4,6-triene-3,17-dione (9) was converted into the 6α,7α-difluoro-adduct (11). Fluorination with CF_3OF led to an increased yield of the adduct (11) and also afforded the 6α-trifluoromethoxy-7α-fluoro-adduct (12). Dehydrofluorination of the latter gave 6-trifluoromethoxyandrosta-1,4,6-triene-3,17-dione (13). 21-Acetoxy-11β,17α-dihydroxypregna-1,4,6-triene-3,20-dione (5) was prepared by stepwise dehydrogenation of cortisol acetate (14). Subsequent low temperature treatment with CF_3OF resulted in two major products, formulated as the adducts (17) and (18).

ALTHOUGH it is firmly established that enolic derivatives of steroidal enones may be efficiently fluorinated under mild conditions with CF_3OF,[1,2] few examples of the electrophilic addition of fluorine, either directly or indirectly, to electron-deficient double bonds are reported in the literature. Of these, the reactions of CF_3OF with testosterone [3] and glycyrrhetic acid enone,[4] and the reported conversion of cholestenone into the 4α,5α-difluoro-adduct with molecular fluorine,[5] are particularly worthy of note. Our interest in selective fluorination processes [1,3,6] with potential application to the synthesis of pharmaceutically important fluorinated corticosteroids led us to examine the direct fluorination of diverse steroidal 16-en-20-ones and 1,4,6-trien-3-ones as a means of introducing fluorine substituents at C-6, C-7, C-16, and C-17. Herein are reported some of the results of this study.

The introduction of fluorine at C-16 and/or C-17 of steroids has previously been accomplished *inter alia* by opening of a 17,20-epoxide with HF [7] (the corresponding opening of 16,17-epoxide results mainly in rearrangement products), by the addition of BrF (with HF–*N*-bromosuccinimide) to a 16,17-double bond,[8] by treatment of a 16-hydroxy-derivative with $Et_2N{\cdot}CF_2{\cdot}CHFCl$,[9] and by reaction of perchloryl fluoride with 17,20-olefinic ethers.[10] Significantly, enhanced reactivity has been observed for derivatives of steroidal 16-en-20-ones,[11] which can be attributed to a favourable release of ring strain accompanying saturation of the *trans*-fused cyclopentene moiety. We reasoned that electrophilic addition of molecular fluorine to the 16,17-double bond of such a system to afford a 16,17-difluorinated product should therefore be feasible. Indeed, treatment of 3β-acetoxy-5α,6β-dichloropregn-16-en-20-one (1) [12] in $CFCl_3$ solution with fluorine at low temperature, in the presence of sodium fluoride as HF scavenger, gave a mixture containing two major products, readily separable by chromatography on Florisil.

The less polar component (40%) was identified as the expected 16α,17α-difluoro-adduct (2). Although the data obtained for this compound clearly showed the presence of a 17α-fluoro-substituent, the configuration of the fluorine at C-16 was uncertain. The final assignment as α was therefore based on the known tendency of fluorine to add predominantly in a *cis*-fashion to alkenes, even in flexible acyclic cases.[5,13] Moreover, electrophilic attack by fluorine was reasonably expected to occur at the α-face of the substrate, on steric grounds. The subsequent conversion of the adduct (2) into 16α,17α-difluoroprogesterone (5), a compound of potential biological activity, also provided further indirect structural confirmation. Thus, treatment of the adduct (2) with

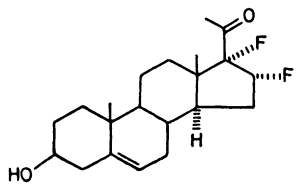


SCHEME

zinc–acetic acid followed by methanolic sodium hydroxide, effected ring-*B* dechlorination and hydrolysis of the 3β-acetoxy-function respectively, to furnish 16α,17α-difluoropregnenolone (4) in 83% overall yield. Our initial attempts to oxidise this compound using either Jones' reagent or pyridinium chlorochromate were uniformly unsuccessful. However, modified Oppenauer oxidation, with *N*-methyl-4-piperidone as hydrogen acceptor,[14] furnished the desired progesterone derivative (5), albeit in modest yield (40%). A superior yield of 83% was subsequently obtained using the procedure of Swern *et al.*[15]

The structural assignment of the second, more polar fluorination product, isolated in 12% yield, followed from physical and spectral data. Although the mass spectrum did not show a molecular ion, the compound was formulated as $C_{23}H_{32}Cl_2F_2O_5$ on the basis of its microanalysis, and was thus isomeric with the difluoro-adduct (2). The absence of an enone chromophore was evident from the u.v. spectrum, and i.r. spectroscopy showed strong absorbances at 1 740 and 1 710 cm^{-1}, attributable to a 3-acetoxy-function and to a C-20 carbonyl group lacking an adjacent fluorine substituent, respectively. In addition, the C-18 methyl resonance (^1H n.m.r.) occurred at δ 1.08, significantly downfield relative to the starting enone (1), and the C-21 methyl signal, although not shifted in this respect, was split into a doublet (*J* 2 Hz). The C-16 vinyl proton resonance was absent, and a double doublet (*J* 53 and 4 Hz), centred at δ 5.03, indicated a geminal (but not a vicinal) fluorine substituent. Furthermore, the ^{19}F n.m.r. spectrum showed two broad multiplets at ϕ^* 130 (width 125 Hz) and 175 (width 130 Hz). Most reasonably the product possessed the rearranged structure (3), the observed large negative optical rotation adding support to the proposed assignment of configuration at C-17. Clearly the mechanism of formation involved a [1,2] methyl shift from C-13 to C-17, in a reaction reminiscent of the Kagi–Miescher rearrangement.[16] We favour the processes outlined in the Scheme, in which the initially formed α-face complex can either collapse to give the normal addition product [3,5,13] (12) (pathway *a*), or undergo a rearrangement involving quenching of the partial positive charge on C-17 by a β-face [1,2] methyl shift with concerted nucleophilic attack by fluoride (pathway *b*). Strong presumptive evidence against the proposal that the product of rearrangement (3) arose from the adduct (2) itself under the reaction conditions, was provided by the observation that both products appeared in the early stages of the reaction, and could be isolated together even before completion of reaction. Interestingly, the use of the less reactive CF_3OF led principally to rearrangement and by-product formation.

The work of Taub *et al.*,[17] however, indicated that 11β-hydroxy-9α-fluoro-corticoids were more prone to Kagi–Miescher rearrangement than were the corresponding 11-oxo-derivatives. It was considered that this difference in reactivity might be attributed to the greater electron-withdrawing effect of the C-11 oxo-function, which would tend to retard inductively a C-18 methyl migration to C-17. Alternatively, an sp^2 centre at C-11 might disfavour the concomitant formation of a 13,14-double bond. Application of this rationale to the present study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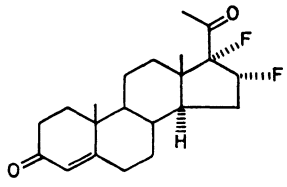
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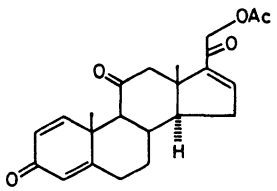
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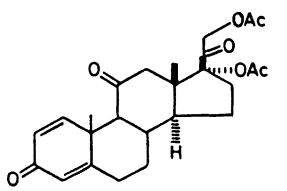
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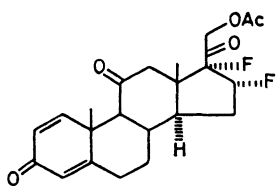
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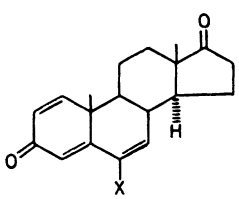
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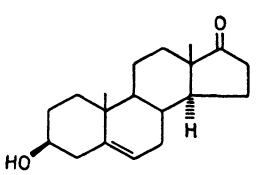
(13) X = OCF_3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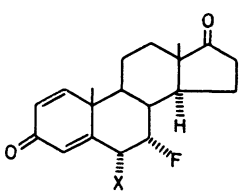
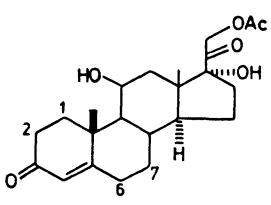
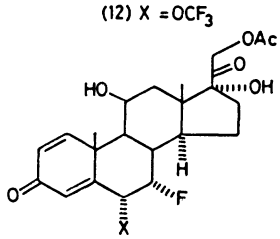

(11) X = F
(12) X = OCF_3


(15)
(14) 1,6-diene
(16) 6-ene


(17) X = F
(18) X = OCF_3

suggested that the presence of an 11-oxo-group in the corticoid (6) should render it less susceptible to rearrangement upon fluorination. As a consequence, selective fluorination of the more reactive 16,17-double bond was expected to predominate, even in the presence of the ring-*A* cross-conjugated dienone system. Accordingly, the corticoid (6) was prepared in 51% yield from 17α,-

21-diacetoxypregna-1,4-diene-3,11,20-trione (7),[18] by treatment with potassium acetate in dimethylformamide at 105 °C. Passage of 3.5 equiv. of fluorine through a solution of the corticoid (6) in CF_3CH_2OH containing HF scavenger, at −40 °C, gave an incomplete reaction. Work-up and repeated chromatography afforded starting material (35%), a complex mixture of ring-*A*-fluorinated products (^1H n.m.r. evidence) (*ca.* 30%), and the desired difluoro-adduct (8) (10%). The structure was assigned from physical and spectral data, which were essentially analogous to those of the major product of fluorination of the enone (1). No evidence was obtained for the formation of a product of rearrangement; the poor yield (based on conversion of starting material) was evidently a result of competitive fluorination of ring *A*.

The feasibility of the direct fluorination of steroidal 1,4,6-trien-3-ones as a possible route to the pharmaceutically interesting 6α-fluoro-corticosteroids was also examined. We have previously demonstrated that various 1,4-dien-3-ones may be efficiently converted *via* 1,3,5-triene-3-esters into predominantly 6β-fluoro-substituted derivatives, on treatment with CF_3OF.[19] It was envisaged that in the case of the 1,4,6-trien-3-one system, reaction with fluorine or CF_3OF might lead directly to 6α,7α-disubstituted products, arising from preferred α-face attack by the reagent at the least deactivated 6,7-double bond. The substrate chosen to test this hypothesis was androsta-1,4,6-triene-3,17-dione (9), prepared in 45% yield by dehydrogenation of the readily available 3β-hydroxy-5-androsten-17-one (dehydroepiandrosterone) (10) with dichlorodicyanobenzoquinone in refluxing dioxan. Fluorination of the trienone (9) in CF_3CH_2OH at −40 °C resulted in a complex mixture, from which chromatography afforded starting material (23%) and a difluoro-adduct (10%), formulated as the 6α,7α-difluoro-isomer (11). The integrity of the ring-*A* cross-conjugated dienone moiety in (11) was evident from spectral data [*inter alia* $\lambda_{max.}$ 240 nm (ν 17 000); $\nu_{max.}$ 1 660 and 1 630 cm^{-1}] thus confirming saturation of the 6,7-double bond. Furthermore, the ^1H n.m.r. spectrum [δ 0.95 (s, 18-H_3), 1.30 (s, 19-H_3), 4.4—6.0 (2 H, m, 6-, 7-H_2), 6.33 (1 H, dd, *J* 10 Hz, 2-H), 6.53 (1 H, br, s, 4-H), and 7.10 (1 H, dd, *J* 10 Hz, 1-H)] was consistent with a 6α-fluoro-substituent (6β-fluoro-4-en-3-ones have been shown to exhibit doublets for both the C-19 methyl protons and the 4-proton,[20] and long-range coupling between a 6α-fluorine and 1-proton of 1,4-dienones has precedent [19,21]). The final assignment of configuration of the 7-fluoro substituent as α was made by comparison of the complex pattern due to the 6- and 7-protons (δ 4.4—6.0) with calculated spectra for both C-7 epimers.

In contrast, the corresponding reaction with CF_3OF at −20 °C went to completion, with the formation of two major products. Repeated chromatography yielded a difluoro-adduct (15%) identical with the product (11) of the reaction with fluorine, and a fully characterised CF_3OF adduct (12) (30%). Similar results were obtained when the reaction was carried out in the presence of the radical inhibitor nitrobenzene, and it was concluded that the unselective ring-*A* reactions were not radical in nature. The CF_3OF adduct (12), on refluxing with 1,5-diazabicyclo[5.4.0]undec-5-ene in benzene solution, underwent preferential elimination of hydrogen fluoride to furnish the corresponding 6-trifluoromethoxy-1,4,6-triene-3,17-dione (13) in 56% yield after recrystallisation, thus providing confirmation of the assigned regiochemistry for the adduct (12) at C-6 and C-7.

Finally, the successful addition of CF_3OF to the trienone (9) prompted us to apply this reaction to the corticoid analogue 21-acetoxy-11β,17α-dihydroxypregna-1,4,6-triene-3,20-dione (15). Attempted synthesis of this compound *via* direct dehydrogenation of the readily available hydrocortisone acetate (14) with chloranil in t-butyl alcohol under reflux afforded only the known [22] 4,6-dien-3-one (16) (70—80%). Subsequent treatment of this product with dichlorodicyanobenzoquinone in refluxing dioxan, however, produced the required trienone (15) in 30—35% overall yield. Addition of 1.4 equiv. of CF_3OF in $CFCl_3$ solution to a cooled (−78 °C) solution of the trienone (15) in dichloromethane containing 4% methanol (to minimise reaction of the 11β-hydroxy-group) and calcium oxide as HF scavenger, resulted in complete loss of starting material (u.v. and t.l.c. analysis). Extensive chromatography of the crude product mixture provided the 6α,7α-difluoro-adduct (17) (14%) and the corresponding CF_3OF adduct (18) (25%). The spectral data of the two corticoid adducts were essentially analogous to those of the corresponding androstane derivatives (11) and (12); regio- and stereochemical assignments were made accordingly.

Thus the direct *cis*-addition of molecular fluorine, or of CF_3OF, to even deactivated ethylenic linkages provides an interesting method for the introduction of fluorine and/or trifluoromethoxy-groups into biologically active molecules.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. Optical rotations were recorded at room temperature using a Rudolph photoelectric polarimeter, and refer to chloroform solutions (unless otherwise stated). I.r. spectra were recorded with a Perkin-Elmer 137 Infracord spectrophotometer and are reported for KBr discs (unless otherwise stated). U.v. spectra were recorded with a Cary 11 spectrophotometer and are reported for ethanolic solutions. N.m.r. spectra (^1H and ^{19}F) were recorded with a Varian T60 spectrometer for solutions in $CDCl_3$ (unless otherwise stated); chemical shifts are reported downfield from internal Me_4Si (δ) and upfield from internal $CFCl_3$ (φ*), respectively. Medium-pressure column chromatography was carried out on Merck Kieselgel H silica gel. P.l.c. and t.l.c. were carried out on Merck GF_{254} silica gel. Developing solvents are given in parentheses. Fluorination procedures were as previously described.[6]

Reaction of 3β-*Acetoxy*-5α,6β-*dichloropregn*-16-*en*-20-*one* (1) *with Fluorine*.—Fluorine (*ca.* 10 mmol), diluted to 5% with nitrogen, was passed into a vigorously stirred solution of the enone (1) (1.30 g, 3.0 mmol) in $CFCl_3$ (400 ml) containing sodium fluoride (5 g), at −78 °C, until reaction was complete (t.l.c.). The mixture was flushed with nitrogen and

worked up with sodium thiosulphate solution to give a crude product. The reaction was repeated three times to give a total of 4.00 g. Column chromatography on Florisil (eluant benzene–ethyl acetate) gave 3β-*acetoxy*-5α,6β-*dichloro*-16α,17α-*difluoropregnan*-20-*one* (2) (1.61 g, 40%), m.p. 212—214 °C (from methanol), $[\alpha]_D$ −19.3° (*c* 8.0); $\nu_{max.}$ 3 000, 1 740, 1 720, 1 370, 1 265, 1 245, and 1 225 cm^{-1}; δ ($CDCl_3$) 0.75 (s, 18-H_3), 1.30 (s, 19-H_3), 2.05 (s, OAc), 2.27 (d, *J* 6 Hz, 21-H_3), 4.35 (1 H, m, 6-H), 5.23 (1 H, br, m, 3-H), and 5.58 (1 H, br, dd, *J* 50 and 17 Hz, 16-H); δ (C_6D_6) 0.45 (s, 18-H_3), 1.12 (s, 19-H_3), 1.77 (s, OAc), 1.98 (d, *J* 6 Hz, 21-H_3), 4.03 (1 H, m, 6-H), 5.42 (1 H, br, m, 3-H), and 5.67 (1 H, m, *J* 50, 17, 8, and 3 Hz, 16-H); ϕ* 182.8 (m, width 50 Hz, 17-F) and 197.6 (br, quintet, spacing 27 Hz, 16-F); *m/z* 464 (3%) ($M^{+\cdot}$), 429 (10), 405 (10), 368 (40), and 333 (100) (Found: C, 58.8; H, 6.9; Cl, 15.5; F, 8.1. $C_{23}H_{32}Cl_2F_2O_3$ requires C, 59.35; H, 6.9; Cl, 15.2; F, 8.2%); and 3β-*acetoxy*-5α,6β-*dichloro*-13α,16α-*difluoro*-17β-*methyl*-18-*nor*-17α-*pregnan*-20-*one* (3) (620 mg, 12%), m.p. 188 °C (decomp.) (from methanol); $[\alpha]_D$ −76°; $\nu_{max.}$ 3 000, 1 740, 1 710, 1 360, and 1 240 cm^{-1}; δ 1.08 (s, 17-CH_3), 1.33 (s, 19-H_3), 2.02 (s, OAc), 2.32 (d, *J* 2 Hz, 21-H_3), 4.40 (1 H, m, 6-H), 5.33 (1 H, br, m, 3-H), and 5.03 (1 H, dd, *J* 53 and 4 Hz, 16-H); ϕ* 130 (m, width 124 Hz, 16-F) and 175 (m, width 131 Hz, 13-F); *m/z* 404 (14%), 402 (80), 384 (68), 382 (100), 306 (76), 271 (76), and 111 (100) (Found: C, 59.9; H, 6.9; Cl, 15.3; F, 8.4. $C_{23}H_{32}Cl_2F_2O_5$ requires C, 59.35; H, 6.9; Cl, 15.2; F, 8.2%).

16α,17α-*Difluoro*-3β-*hydroxypregn*-5-*en*-20-*one* (4).—The difluoro adduct (2) (1.34 g, 2.9 mmol) in ethanol (300 ml) containing zinc (5.3 g, 81 mmol) and acetic acid (1 ml) was refluxed for 3 h. Filtration and aqueous work-up gave crude product (1.10 g, 95%), which was hydrolysed in methanol (200 ml) containing water (1 ml) and sodium hydroxide (500 mg, 12.5 mmol) over 1 h. Acidic work-up afforded a crude product (910 mg, 95%) which after column chromatography and h.p.l.c. (eluant benzene–ethyl acetate) gave *compound* (4) (248 mg, 28%). Repetition on a smaller scale [450 mg of adduct (2)] led to an increase in yield (280 mg, 83%); m.p. 151—154 °C; $[\alpha]_D$ −10° (*c* 10.0); $\nu_{max.}$ 3 350, 3 000, 1 720, 1 350, and 1 050 cm^{-1}; δ 0.73 (s, 18-H_3), 1.05 (s, 19-H_3), 2.32 (d, *J* 6 Hz, 21-H_3), 3.60 (1 H, br, m, 3-H), 5.42 (1 H, m, 6-H), and 5.70 (1 H, m, *J* 50, 16, and 5 Hz, 16-H); ϕ* 183 (m, width 65 Hz, 17-F) and 198.0 (quintet of doublets, spacing 27 and 9 Hz, 16-F); *m/z* 352 (87%, $M^{+\cdot}$), 334 (100), 319 (96), 267 (58), 145 (40), and 108 (56) (Found: C, 70.1; H, 8.5; F, 10.4. $C_{21}H_{30}F_2O_3,0.5H_2O$ requires C, 69.8; H, 8.6; F, 10.5%).

Oxidation of Difluoropregnenolone (4) (in collaboration with Dr. D. Alker).—To oxalyl chloride (0.2 ml, 2.2 mmol) in dichloromethane (40 ml) at −60 °C was slowly added dimethyl sulphoxide (0.34 ml, 4.8 mmol) in dichloromethane (5 ml). The resulting solution was allowed to warm to −45 °C, and then a solution of difluoropregnenolone (4) (228 mg, 0.65 mmol) in dichloromethane (10 ml) was added dropwise at such a rate that the temperature was maintained at −45 °C. The mixture was stirred for 15 min at −45 °C, triethylamine (1 ml, 7.2 mmol) was added dropwise, and then stirring was continued at −45 °C for a further 5 min. Dilution with dichloromethane (70 ml) and acidic work-up yielded crystalline material which was refluxed in ethanol (15 ml) containing oxalic acid (46 mg) for 5 min. Evaporation, followed by medium-pressure chromatography (eluant hexane–ethyl acetate) gave 16α,17α-*difluoroprogesterone* (5) (190 mg, 83%), m.p. 187—189 °C, $[\alpha]_D$ +140° (*c* 11.0); $\nu_{max.}$ 3 050, 1 730, 1 670, and 1 360 cm^{-1}; $\lambda_{max.}$ 238 nm (ε 15 500); δ 0.77 (s, 18-H_3), 1.22 (s, 19-H_3), 2.30 (d, *J* 6 Hz, 21-H_3), 5.63 (1 H, m, *J* 50, 17, and 5 Hz, 16-H), and 5.79 (1 H, s, 4-H); δ (C_6D_6) 0.52 (s, 18-H_3), 0.73 (s, 19-H_3), 2.03 (d, *J* 6 Hz, 21-H_3), 5.70 (1 H, m, *J* 51, 18, 7, and 4 Hz, 16-H), and 5.72 (1 H, s, 4-H); ϕ* 183.4 (m, width 59 Hz, 17-F), and 198.2 (quintet of doublets, spacing 26 and 9 Hz, 16-F); *m/z* 351 (100%, $M^{+\cdot}$), 309 (90), and 43 (80) (Found: C, 71.8; H, 7.9; F, 10.5. $C_{21}H_{28}F_2O_2$ requires C, 72.0; H, 8.05; F, 10.8%).

21-*Acetoxypregna*-1,4,16-*triene*-3,11,20-*trione* (6).—17α,21-Diacetoxypregna-1,4-diene-3,11,20-trione (7) [18] (1.83 g, 4.1 mmol) was stirred in dimethylformamide (15 ml) containing potassium acetate (0.88 g, 9 mmol) at 105 °C under argon for 5.5 h. Aqueous work-up gave a yellow foam (1.66 g), which was crystallised from ethyl acetate to afford *compound* (6) (0.81 g, 51%), m.p. 165—166 °C, $[\alpha]_D$ +103° (*c* 10.0); $\nu_{max.}$ 3 000, 1 750, 1 710, 1 680, 1 655, 1 630, 1 230, 1 210, and 1 070 cm^{-1}; $\lambda_{max.}$ 238 nm (ε 24 500); δ 0.95 (s, 18-H_3), 1.47 (s, 19-H_3), 2.17 (s, OAc), 3.08 (d, *J* 13 Hz, 12α-H), 4.97 (2 H, br, s, 21-H_2), 6.12 (1 H, br, s, 4-H), 6.22 (1 H, dd, *J* 10 and 2 Hz, 2-H), 6.87 (1 H, m, 16-H), and 7.78 (1 H, d, *J* 10 Hz, 1-H) (Found: C, 72.2; H, 7.0. $C_{23}H_{26}O_5$ requires C, 72.2; H, 6.85%).

Reaction of 21-*Acetoxypregna*-1,4,16-*triene*-3,11,20-*trione* (6) *with Fluorine*.—Fluorine, diluted to 3% in nitrogen, was passed through a vigorously stirred solution of compound (6) (1.0 g, 2.6 mmol) in CF_3CH_2OH (200 ml) containing 3 Å molecular sieves (3.6 g) at −35 °C. After passage of 3.4 equiv. of fluorine, the mixture was flushed with nitrogen and evaporated. Repeated chromatography of the residue gave, in order of increasing polarity, a non-polar mixture (329 mg) containing ring-*A* fluorination products (^{1}H n.m.r. spectroscopy), a fraction containing the major reaction product (273 mg), and a fraction indicated to be mainly starting material (6) by t.l.c. and ^{1}H n.m.r. spectroscopy (373 mg, 37%). P.l.c. of the middle fraction afforded 21-*acetoxy*-16α,17α-*difluoropregna*-1,4-*diene*-3,11,20-*trione* (8) (120 mg, 11%), which could be further purified by h.p.l.c. and crystallisation from methanol; m.p. 227—237 °C; $[\alpha]_D$ +170° (*c* 4.8); $\nu_{max.}$ 3 500, 3 000, 1 760, 1 740, 1 710, 1 670, 1 630, 1 610, and 1 235 cm^{-1}; $\lambda_{max.}$ 239 nm (ε 14 800); δ 0.77 (s, 18-H_3), 1.43 (s, 19-H_3), 2.18 (s, OAc), 2.87 (d, *J* 13 Hz, 12α-H), 4.85 (2 H, m, 21-H_2), 6.15 (1 H, br, s 4-H), 6.23 (1 H, dd, *J* 10.2 Hz, 2-H), and 7.68 (1 H, d, *J* 10 Hz, 1-H); ϕ* 191 (m, width 60 Hz, 17-F) and 198 (br, m, width *ca.* 140 Hz, 16-F); *m/z* 420 (60%, $M^{+\cdot}$), 392 (29), 376 (100), and 275 (77) (Found: C, 65.2; H, 6.1; F, 9.2. $C_{23}H_{26}F_2O_5$ requires C, 65.7; H, 6.2; F, 9.0%).

Androsta-1,4,6-*triene*-3,17-*dione* (9).—2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (16.5 g, 3.35 equiv.) was added in three portions over 24 h to 3β-hydroxyandrost-5-en-17-one (10) (10.0 g, 34.8 mmol) in refluxing dioxan (200 ml). The resulting mixture was cooled, filtered, and directly chromatographed on alumina (eluant dichloromethane) to give compound (9) (4.4 g, 44%). Recrystallisation from diethyl ether–hexane gave material (3.5 g) of m.p. 162—165 °C (lit.,[23] 164—166 °C); $[\alpha]_D$ +91° (*c* 6.0, dioxan) [lit.,[23] +72.5° (dioxan)]; $\nu_{max.}$ 3 000, 1 740, 1 650, 1 600, 1 380, and 1 280 cm^{-1}; $\lambda_{max.}$ 298 (ε 12 800), 256 (10 500), and 222 nm (12 000); δ 1.00 (s, 18-H_3), 1.22 (s, 19-H_3), 6.05 (1 H, br, s, 4-H), 6.22—6.43 (3 H, m, 2-, 6-, 7-H), and 7.10 (1 H, d, *J* 10 Hz, 1-H).

Reaction of Androsta-1,4,6-*triene*-3,17-*dione* (9) *with Fluorine*.—Fluorine, diluted to 3% with nitrogen, was

passed into a vigorously stirred solution of the trienone (9) (1.50 g, 5.3 mmol) in CF_3CH_2OH (200 ml) containing 4 Å molecular sieves (2 g). After passage of 2.2 equiv. of fluorine, u.v. analysis indicated 20% remaining starting material. The mixture was then flushed with nitrogen and the solvent removed *in vacuo*. Column chromatography of the residue (eluant benzene–ethyl acetate) followed by p.l.c. (eluant 30% ethyl acetate–benzene) gave, in order of increasing polarity, a non-polar mixture (118 mg), the starting trienone (9) (324 mg, 23%), and 6α,7α-*difluoroandrosta*-1,4-*diene*-3,17-*dione* (11) (139 mg, 10%), m.p. 218—219 °C (from acetone–ether–hexane); $[\alpha]_D$ +93° (*c* 4.5); $\nu_{max.}$ 3 000, 1 740, 1 660, and 1 630 cm^{-1}; $\lambda_{max.}$ 240 nm (ε 17 000); δ 0.95 (s, 18-H_3), 1.30 (s, 19-H_3), 4.4—6.0 (2 H, m, 6-, 7-H), 6.33 (1 H, dd, *J* 10 Hz, 2-H), 6.53 (1 H, br, s, 4-H), and 7.10 (1 H, dd, *J* 10 Hz, 1-H); ϕ^* 201 (m, 2 sets of 4 resonances, spacings 47 and 8 Hz, 6-F) and 214.5 (m, width 180 Hz, 7-F); *m/z* 320 (46%, $M^{+\cdot}$), 140 (100), and 139 (59) (Found: C, 71.1; H, 7.1; F, 12.1. $C_{19}H_{22}F_2O_2$ requires C, 71.2; H, 6.9; F, 11.9%).

Reaction of Androsta-1,4,6-*triene*-3,17-*dione* (9) *with Trifluoro(fluoro-oxy)methane*.—Trifluoro(fluoro-oxy)-methane (0.15M-solution in $CFCl_3$ at −78 °C) was added in portions to a solution of the trienone (9) (596 mg, 2.1 mmol) in dichloromethane (100 ml) containing CaO (470 mg, 4 equiv.) at −20 °C. U.v. and t.l.c. analysis indicated complete consumption of starting material after a total of 1.56 equiv. of CF_3OF has been added. The mixture was flushed with nitrogen and worked up with sodium thiosulphate solution to give a crude product. Medium-pressure chromatography (eluant 50% dichloromethane–ethyl acetate) and h.p.l.c. (30% ethyl acetate–benzene) gave a non-polar mixture (255 mg), from which was separated 7α-*fluoro*-6α-*trifluoromethoxyandrosta*-1,4-*diene*-3,17-*dione* (12) (248 mg, 30%), m.p. 223—226 °C (from hexane–ethyl acetate); $[\alpha]_D$ +60° (*c* 8.0); $\nu_{max.}$ 3 050, 1 740, 1 660, 1 630, 1 270, 1 230, and 1 160 cm^{-1}; $\lambda_{max.}$ 237 nm (ε 18 500); δ 0.95 (s, 18-H_3), 1.32 (s, 19-H_3), 4.0—6.0 (2 H, m, 6-, 7-H_2), 6.30 (1 H, dd, *J* 10 and 2 Hz, 2-H), 6.52 (1 H, br, s, 4-H) and 7.03 (1 H, d, *J* 10 Hz, 1-H); ϕ^* 57.8, 58.4 (OCF_3), and 211 (quintet, spacing 27 Hz, 7-F); *m/z* 386 (62%, $M^{+\cdot}$), 207 (11), 206 (100), and 205 (79) (Found: C, 62.3; H, 5.7; F, 20.1. $C_{20}H_{22}F_4O_3$ requires C, 62.2; H, 5.7; F, 19.7%). Also isolated was 6α,7α-difluoroandrosta-1,4-diene-3,17-dione (11) (100 mg, 15%).

6-*Trifluoromethoxyandrosta*-1,4,6-*triene*-3,17-*dione* (13).—The CF_3OF adduct (12) (112 mg, 0.29 mmol) was refluxed in benzene (10 ml) containing 1,5-diazabicyclo[5.4.0]undec-5-ene (0.06 ml, 0.41 mmol) for 1 h, after which t.l.c. indicated complete reaction. The mixture was concentrated and separated by p.l.c. (eluant 30% ethyl acetate–diethyl ether) to give *compound* (13) (92 mg, 87%), m.p. 155—157 °C (from aqueous methanol); $[\alpha]_D$ −21° (*c* 6.0); $\nu_{max.}$ ($CHCl_3$) 3 050, 1 740, 1 660, 1 615, 1 250, 1 190, and 1 170 cm^{-1}; $\lambda_{max.}$ 289 (ε 10 500) and 259 nm (ε 11 600); δ 1.02 (s, 18-H_3), 1.30 (s, 19-H_3), 6.10 (1 H, br, s, 4-H), 6.37 (1 H, dd, *J* 10 and 2 Hz, 2-H), 6.50 (1 H, br, s, 6-H), and 7.18 (1 H, d, *J* 10 Hz, 1-H); *m/z* 366 (100%, $M^{+\cdot}$) and 149 (51) (Found: C, 65.6; H, 5.7; F, 15.8. $C_{20}H_{21}F_3O_3$ requires C, 65.6; H, 5.8; F, 15.6%).

Reaction of 21-*Acetoxy*-11β,17α-*dihydroxypregna*-1,4,6-*triene*-3,20-*dione* (15) *with Trifluoro(fluoro-oxy)methane*.—Trifluoro(fluoro-oxy)methane (0.34M-solution in $CFCl_3$ at −78 °C) was added in portions to a stirred solution of the trienone (15) (744 mg, 1.86 mmol) in dichloromethane (48 ml) and methanol (2 ml) containing CaO (413 mg, 4 equiv.) at −78 °C. After addition of 1.4 equiv. of CF_3OF, the trienone triple u.v. maxima had coalesced to a single maximum at 238 nm. T.l.c. indicated complete consumption of the trienone (15) to give two major, less polar products. The mixture was flushed with argon and filtered through Celite, and the solvent removed *in vacuo* to give a foam (970 mg). Medium-pressure column chromatography (eluant dichloromethane–ethyl acetate) followed by h.p.l.c. (eluant 50% benzene–ethyl acetate) gave 21-*acetoxy*-7α-*fluoro*-11β,17α-*dihydroxy*-6α-*trifluoromethoxypregna*-1,4-*diene*-3,20-*dione* (18) (224 mg, 25%), m.p. 135—139 °C (from dichloromethane); $[\alpha]_D$ +51° (*c* 2.4); $\nu_{max.}$ 3 650, 3 050, 1 760sh, 1 730, 1 660, 1 630, 1 270, 1 225, and 1 150 cm^{-1}; $\lambda_{max.}$ 240 nm (ε 13 900); δ (50% CD_3OD–$CDCl_3$) 0.92 (s, 18-H_3), 1.38 (s, 19-H_3), 2.17 (s, OAc), 4.52 (1 H, m, 11α-H), 4.98 (2 H, br, s, 21-H_2), 4.5—5.5 (m, 6-, 7-H), 6.28 (1 H, dd, *J* 10 and 2 Hz, 2-H), 6.38 (1 H, br, s, 4-H), and 7.38 (1 H, d, *J* 10 Hz, 1-H); δ (CD_3CN) 0.87 (s, 18-H_3), 1.45 (s, 19-H_3), 2.07 (s, OAc), 4.52 (1 H, m, 11α-H), 4.87 (2 H, br, s, 21-H_2), 6.20 (1 H, dd, *J* 10.2 Hz, 2-H), and 7.22 (1 H, d, *J* 10 Hz, 1-H); ϕ^* (1 : 1 CD_3OD–$CDCl_3$) 58.8 (s, CF_3O) and 211 (m, quintet, spacing 27 Hz, 7-F); *m/z* 504 (5%, $M^{+\cdot}$), 221 (31), and 205 (100) (Found: C, 56.9; H, 5.5; F, 14.9. $C_{24}H_{28}F_4O_7$ requires C, 57.1; H, 5.6; F, 15.1%). Also isolated was 21-*acetoxy*-6α,7α-*difluoro*-11β,17α-*dihydroxypregna*-1,4-*diene*-3,20-*dione* (17) (115 mg, 14%), m.p. 220—225 °C (from hexane–ethyl acetate); $[\alpha]_D$ +70° (*c* 3.5); $\nu_{max.}$ 3 600, 3 000, 1 745sh, 1 730, 1 660, 1 630, 1 370, 1 260, and 1 235 cm^{-1}; $\lambda_{max.}$ 240 nm (ε 14 600); δ (20% CD_3OD–$CDCl_3$) 0.95 (s, 18-H_3), 1.53 (s, 19-H_3), 2.22 (s, OAc), 4.57 (1 H, m, 11α-H), 5.03 (br, s, 21-H_2), 4.5—6.2 (m, 6-, 7-H), 6.37 (1 H, dd, *J* 10 and 2 Hz, 2-H), 6.43 (1 H, br, s, 4-H), and 7.45 (1 H, dd, *J* 10 and 2 Hz, 1-H); δ (CD_3CN) 0.87 (s, 18-H_3), 1.43 (s, 19-H_3), 2.08 (s, OAc), 4.47 (1 H, m, 11α-H), 4.90 (ABq, *J* 18 Hz, 21-H_2), 4.5—6.2 (m, 6-, 7-H), 6.15 (2 H, m, 2-, 4-H), and 7.23 (1 H, dd, *J* 10 and 2 Hz, 1-H); ϕ^* (20% CD_3OD–$CDCl_3$) 201.5 (2 m, spacing 40 Hz, 6-F) and 214 (br, m, width 190 Hz, 7-F); *m/z* 438 (6%, $M^{+\cdot}$), 171 (28), 149 (44), 139 (35), and 132 (100) (Found: C, 63.0; H, 6.5; F, 8.6. $C_{23}H_{28}F_2O_6$ requires C, 63.0; H, 6.4; F, 8.7%). A complex mixture of non-polar by-products was also isolated (445 mg).

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